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July 8, 1998

Confidential pursuant to 5 USC 552;
18 USC 1905; 21 USC 331 (j); 21
CFR 314.30 and 20.61.

Murray M. Lumpkin, M.D.
Deputy Center Director for Review
Management
Center for Drug Evaluation & Research
1451 Rockville Pike, Rm. 6027 (HFD-001)
Rockville, MD 20852

Dear Dr. Lumpkin:

I am writing this letter on behalf of my client, CollaGenex Pharmaceuticals, Inc...to follow up on an earlier letter and my recent discussion with Mr. Morrison regarding the regulatory status of CollaGenex' product Periostat®. As you know, FDA has been reviewing CollaGenex' NDA for Periostat® as an antibiotic application under the now repealed section 507 of the Food, Drug, and Cosmetic Act ("FDCA"). CollaGenex believes that Periostat® should be approved under the new drug provisions in section 505 of the FDCA. The distinction is important because Periostat® will not be eligible for market exclusivity if it is approved as an antibiotic. Given the fact that Periostat® does not kill or inhibit microorganisms, it seems both counterintuitive and potentially confusing to treat it as an antibiotic. Further, there is no legal reason to do so; Periostat® does not fit the legal definition of an antibiotic because, among other reasons, it does not have the capacity to inhibit or destroy microorganisms. It seems particularly unnecessary to designate Periostat® as an antibiotic at a time when Congress has abolished the legal distinction between section 505 drugs and section 507 antibiotics. This letter explains why CollaGenex believes it is only appropriate to approve Periostat® under section 505.

Periostat® (doxycycline hyclate capsules, U.S.P., 20 mg.) is intended to be used as an adjunct to scaling and root planing to promote and maintain periodontal attachment level gain and to reduce pocket depth and bleeding on probing in patients with adult periodontal disease. It is recommended for long-term daily use (up to one year). Periostat® inhibits matrix metalloproteinases (collagenase, gelatinase, etc.), enzymes that cause connective tissue breakdown. Thus, it disrupts the chronic progressive tissue breakdown characteristic of periodontal disease.

Periostat® is not intended to nor does it destroy or inhibit microorganisms. To be sure, in dosages substantially higher than those in Periostat®, doxycycline has an antimicrobial effect, and doxycycline is approved for that use at dosages of 50 mg. twice daily and above. At the 20

mg. dosage in Periostat[®], however, doxycycline does not destroy or inhibit microorganisms, providing a serum doxycycline concentration substantially below the minimum serum level of 1.0 microgram/ml needed for an antimicrobial effect. More information on studies of Periostat's[®] ability (actually, its lack thereof) to destroy or inhibit microorganisms has been provided previously in the Periostat[®] NDA and in the attached letter from Edward Korwek, submitted last September on CollaGenex' behalf. Also attached are abstracts of two forthcoming articles that provide additional information showing that Periostat[®] is not antimicrobial.

An NDA for Periostat[®] was submitted under section 505 in August 1996. The product was assigned for review to CDER's Division of Dermatologic and Dental Drug Products. Before filing the application, FDA requested that CollaGenex amend its cover letter to state that the application was being submitted under section 507. Although CollaGenex did not concur with FDA's determination that Periostat[®] is an antibiotic, the company submitted the revised cover letter, with the expressed intention of revisiting the designation issue at a later date. In September 1997, Mr. Korwek submitted the attached letter requesting that the Periostat[®] application be redesignated under section 505. During my recent conversation with Mr. Morrison, I agreed to renew in writing CollaGenex's previous request.

The FDCA defines an antibiotic as

"any drug intended for use by man containing any quantity of a chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance)."¹

The definition clearly contemplates that quantity matters. To be an antibiotic, a drug must contain a "quantity of a chemical substance ... which has the capacity to inhibit or destroy microorganisms in dilute solution." A quantity of drug that does not have the capacity to inhibit or destroy microorganisms would not fit the definition.² Thus, if Periostat[®] has the capacity to inhibit or destroy microorganisms in dilute solution, it is an antibiotic; otherwise, it is not. FDA has satisfied itself that doxycycline capsules containing 50, 100, or 300

1. Former FDCA § 507(a); former 21 U.S.C. 357(a); now FDCA § 201(jj); 21 U.S.C. 321(jj).

2. An alternate reading, that the statute meant to encompass as an antibiotic a chemical substance if any quantity could destroy microorganisms, appears far less plausible. Had Congress meant that the law be interpreted this way, it could have eliminated the reference to quantity altogether so that the statute said that any drug containing a chemical substance produced by a microorganism and which has the capacity to inhibit microorganisms in dilute solution is an antibiotic. As a matter of statutory construction, the reference to quantity in the antibiotic definition has meaning only if it refers to the quantity in the drug at issue.

milligrams of doxycycline inhibit or destroy microorganisms in dilute solution: FDA's regulation establishing an antibiotic standard at these strengths makes that clear.³ Periostat®, however, which contains doxycycline at a significantly lower strength, would not meet the test, in that at serum levels as administered according to Periostat's labeling, it will not kill or inhibit microorganisms even at full labeled strength, much less when diluted. Thus, even though doxycycline may be an antibiotic in some products, it is not an antibiotic in Periostat.®

Even if one were to conclude as a matter of law that Periostat® could fall within the definition of an antibiotic, FDA could, and in my view should, still decide to approve it under section 505. There are several precedents for doing so. One obvious example is preservatives. Although some products contain ingredients that would be antibiotics at a higher dosage level, when the same ingredient is used for preservative purposes, FDA does not treat the product as an antibiotic.⁴ Similarly, both Lorabid® (loracarbef), approved in 1991, and Azactam (aztreonam), approved in 1986, which are the subject of antibiotic monographs, were approved under section 505.

Perhaps the best reason to treat Periostat® as a section 505 drug is common sense. Both medical professionals and consumers understand that antibiotics are products intended to destroy or inhibit microorganisms. Virtually every text we have identified proceeds on such assumptions. Stedman's medical dictionary, for example, defines antibiotic as "a soluble substance derived from a mold or bacterium that inhibits the growth of other microorganisms."⁵ Similarly, Goodman and Gilman define antibiotic as a substance produced by various species of microorganisms that suppress the growth of other microorganisms and eventually may destroy them.⁶ In the past, FDA has expressed the same view. One need look no further than the OTC rulemaking for Topical Antibiotic Products to see that this is the case. In its tentative final monograph, FDA interpreted the term antibiotic to refer to a product that has the capacity to inhibit or destroy microorganisms and concluded that "... it would be misleading to allow marketing of an antibiotic containing drug product without labeling that

3. 21 CFR 446.120a. ("Doxycycline hyclate capsules are composed of doxycycline hyclate and one or more suitable and harmless lubricants and diluents enclosed in a gelatin capsules. Each capsules contains doxycycline hyclate equivalent to either 50, 100, or 300 milligrams of doxycycline.") (regulation to be revoked September 24, 1998 as part of implementation of the FDA Modernization Act of 1997).

4. See, e.g., 21 CFR 433.22. Biologic drugs that contain antibiotics as preservatives (regulation to be revoked September 24, 1998 as part of implementation of the FDA Modernization Act of 1997).

5. Stedman's Medical Dictionary, 25th Edition (1990).

6. Goodman and Gilman, The Pharmacological Basis of Therapeutics, ninth edition, p. 1029.

Murray M. Lumpkin, M.D.

July 8, 1998

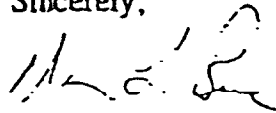
Page 4

indicates the product has microbial activity.⁷ Treating Periostat® as an antibiotic when it has no antimicrobial effect would likewise be misleading.

The FDA Modernization Act of 1997 makes the common sense approach even stronger. Because the distinction between antibiotics and drugs has been eliminated, FDA need not be concerned about the precedential effect of its decision on this product or about whether it is effectuating the intent of the Congress. Both Congressional intent and the future treatment of antibiotic products is clear.

CollaGenex appreciates your willingness to look at this issue. I will call you shortly to follow up.

Sincerely,



Nancy L. Buc

cc: NDA 50-744

7. FDA. Topical Antimicrobial Drug Products for Over-the-Counter Human Use: Tentative Final Monograph. 47 Fed. Reg. 29986, 29988, 29991 (July 9, 1982).

HOGAN & HARTSON
LLP

RECEIVED IN HF-7
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September 11, 1997

Ms. Amanda Bryce Norton
Chief Mediator and Ombudsman
Office of the Commissioner
Room 14-105, HF-7
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

BY HAND DELIVERY

Re: Periostat® NDA 50-774; Request for Designation

Dear Ms. Bryce Norton:

This request is submitted on behalf of our client, CollaGenex Pharmaceuticals, Inc. ("CollaGenex" or the "Company"). We hereby respectfully ask that the Food and Drug Administration ("FDA" or the "agency") designate the above referenced drug, which is the subject of a pending new drug application ("NDA"), as subject to the provisions of section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), 21 U.S.C. § 355(b).

While we recognize this is not a typical designation request that is submitted under 21 C.F.R. Part 3, it nonetheless involves a significant product jurisdictional question appropriate for resolution by the Ombudsman's office. The precise issue addressed herein is whether Periostat® is properly subject to the antibiotic provisions of section 507 of the FDC Act, 21 U.S.C. § 357. In this regard, Periostat® does not meet the statutory definition of an "antibiotic drug." It is a synthetic drug that is neither intended for use as an antimicrobial drug product nor is it capable of inhibiting or destroying microorganisms at the dose levels that are utilized for periodontal disease. Therefore, Periostat® should not be subject to the antibiotic provisions of section 507 of the FDC Act.

MEMPHIS LONDON MONROVIA PARIS PRAGUE WARSAW

BALTIMORE MD BETHESDA MD CHICAGO ILLINOIS CO DENVER CO MCLEAN VA

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Further in connection with this designation request, we respectfully request a waiver of 21 C.F.R. § 3.10, assuming the applicability of 21 C.F.R. Part 3 to this request. This provision provides that the application review clock is stayed during the pendency of review by the product jurisdiction officer. Since this request does not pertain to which center(s) within FDA should have primary jurisdiction, but rather to which section of the FDC Act is pertinent to the approval of Periostat®, no reasons exist to stay the review of the pending NDA for Periostat® because of the submission of this designation request. Any decision in response to this petition will not affect jurisdiction of the Center for Drug Evaluation and Research ("CDER"), which is responsible for review of the NDA for Periostat®. We assume therefore that the waiver request has been granted upon the acceptance for filing of this designation request by FDA, unless we hear otherwise. Note that if this request is not granted upon acceptance of this petition for filing, then you should consider this submission withdrawn.

In accordance with 21 C.F.R. § 3.7, the following information is submitted:

IDENTITY OF SPONSOR

CollaGenex Pharmaceuticals, Inc.
301 S. State Street
Newton, PA 18940

Establishment Registration Number: Not applicable.

Company Contact Person: Mr. Christopher V. Powala
Director, Drug Development &
Regulatory Affairs

Telephone No.: 215-579-7388, extension 16

Facsimile No.: 215-579-8577

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PRODUCT DESCRIPTION

Classification Name:

Not applicable.

Common, Generic, or Usual Name:

Doxycycline hyclate capsules USP (20 mg.)

Proprietary Name:

Periostat®.

Chemical, Physical, or Biological Composition:

Each Periostat® capsule is formulated to contain 20 mg of doxycycline hyclate USP as the only active ingredient.

Status and Brief Reports of Development Work:

With respect to the indicated use of doxycycline that is the subject of this request, in 1983, it was demonstrated that a semisynthetic tetracycline, minocycline, could inhibit collagen breakdown in the uncontrolled diabetic germ-free rat model of periodontal disease by a mechanism independent of its antimicrobial properties (Vol. 2.2, pp. 21-26). Further studies illustrated that this effect was achieved by blocking host-derived matrix metalloproteinases ("MMPs") (collagenase) and thus inhibiting bone and collagen loss. Animal studies have demonstrated that the tetracyclines, which have been chemically altered to render the molecule to be devoid of any anti-microbial activity, also

Since it is impossible to include copies of all of the referenced information without exceeding the page limitations specified at 21 C.F.R. § 3.7(c), we are providing instead general citations to relevant volumes of the NDA 50-744 for Periostat®.

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inhibit other matrix metalloproteinases, such as gelatinase and macrophage elastase, and thus can inhibit connective tissue destruction by a non-antimicrobial mechanism (Vol. 2.5, pp. 4-155). It also was found that doxycycline was the most potent inhibitor of MMPs of all the commercially available tetracyclines.

It has been shown in clinical studies that collagenase activity was reduced in gingival crevicular fluid as well as in adjacent gingival tissue after 14 days of 20 mg b.i.d. doxycycline hyclate administration (Vol. 2.109, pp. 1-8; 91-101). During a 12-week study evaluating the effects of doxycycline hyclate, 20 mg b.i.d. and placebo in patients with adult periodontitis, it was demonstrated that

- No significant changes in gingival inflammation occurred, but there was a significant reduction of gingival crevicular fluid flow, an indication of MMP activity;
- Clinical parameters of tissue breakdown, i.e., clinical attachment level and pocket depth, were significantly improved;
- Gingival crevicular fluid collagenase activity was statistically significantly reduced by 47.3 percent;

Description of Manufacturing Process:

CollaGenex relies on third-party contract manufacturers to produce doxycycline hyclate, the active ingredient in Periostat®, and to manufacture the finished dosage form (Vol. 1.1, CMC Section).

Proposed Use or Indications:

Periostat® is intended for use as a part of a professional oral health program to promote periodontal attachment gain and to reduce bone loss, pocket depth and bleeding on probing in patients with adult periodontal disease (Vol. 202, pp. 1-17).

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Description of Modes of Action:

MMPs are an important family of zinc- and calcium-dependent endopeptidases secreted or released by a variety of host cells (e.g., polymorphonucleocytes, macrophages, bone cells, and fibroblasts) that function at neutral pH and use the various constituents of the extracellular matrix as their substrates. These proteinases are involved in normal physiologic events such as bone remodeling and involution of the post-partum uterus. A variety of pathologic processes are characterized by elevated levels of MMPs, however, giving rise to increased connective tissue breakdown. These disease processes include rheumatoid and osteoarthritis, osteoporosis, and cancer metastasis. In particular, it has been shown that adult periodontitis is accompanied by increased levels of neutrophil collagenase in the gingival crevicular fluid.

Unlike existing treatments which focus on the bacterial infection associated with periodontitis, Periostat®, as a MMP inhibitor, disrupts the chronic progressive tissue degradation characteristic of the disease. As discussed in the Periostat® NDA (Vol. 2.2, pp. 21-26), the active ingredient in Periostat® (doxycycline hyclate) treats periodontitis by inhibiting matrix metalloproteinases (i.e., leukocyte-type and fibroblast-type collagenase, gelatinase, and macrophage elastase) (Vol. 2.5, pp. 4-155). This mechanism of action is independent of the drug's antimicrobial properties at higher dosage levels (Vol. 2.18, pp. 1-50).

As also discussed in the Periostat® NDA, doses below 50 mg q.d. doxycycline hyclate are not effective in providing a measurable antibacterial effect (Vol. 2.18, pp. 1-50). The data and information submitted in support of the Periostat® NDA confirm that doxycycline hyclate at doses of 20 mg. q.d. or 20 mg b.i.d. provide a serum doxycycline concentration below the minimum 1.0 µg/mL doxycycline concentration (Vol. 2.2, p. 77). The results show that plasma concentrations were at a steady state by day 7 for the three treatment groups, with the mean pre-dose plasma doxycycline concentrations at steady state ranging from 0.13 to 0.14 µg/mL, 0.32 to 0.34 µg/mL, and 0.25 to 0.31 µg/mL following 20 mg q.d., 20 mg b.i.d., and 50 mg q.d. dosing, respectively. The mean steady state concentration and the mean steady state maximum concentration values following doxycycline hyclate treatments of 20 mg q.d. and

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20 mg b.i.d. were all statistically significantly lower than 1.0µg/mL, the accepted threshold for antimicrobial activity.

Also, in terms of this request, nonclinical studies cited in the Periostat® NDA using culture plate analysis and speciation via DNA probe analysis showed no anti-bacterial effect of doxycycline hyclate 20 q.d. or 20 mg b.i.d. (Vol. 2.18, pp. 1-50 and Vol. 2.19, Report 5732.11F). No effects were observed on total anaerobic bacteria *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, or *Porphyromonas gingivalis*, *Fusobacteria*, or *Actinomyces* from the periodontium of patients with adult periodontitis.

Recent studies have shown that doxycycline and novel tetracycline analogs chemically modified to render them devoid of antimicrobial activity can inhibit connective tissue breakdown by a variety of direct and indirect mechanisms including (Vol. 2.5, p. 4; Vol. 2.2, pp. 21-26):

1. Direct, non-competitive inhibition of active collagenase, which appears to depend on the Ca++ and Zn++ binding properties of doxycycline;
2. Prevention of the conversion of pro-collagenase to collagenase, which appears to be independent of metal ion binding properties; and
3. Inhibition of the degradation of the serum protein, α_1 -proteinase inhibitor.

Alpha₁-proteinase inhibitor is involved in the inhibition of other tissue destructive enzymes such as elastase which are not directly inhibited by doxycycline. Maintenance of high concentrations of α_1 -proteinase inhibitor in tissue would protect elastase-susceptible connective tissue components such as elastic fibers, fibronectin, and proteoglycans, as well as maintaining high levels of the naturally occurring TIMPs (tissue inhibitors of metalloproteinases), which are also substrates for elastase.

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Schedule and Duration of Use:

Periostat® is recommended for long-term daily use (up to one year) at dose level of 20 mg b.i.d.

Dose and Route of Administration:

Periostat® is intended solely for oral administration.

Description of Related Products and Regulatory Status:

Existing therapies and those treatments known by the Company to be under development for periodontitis are designed primarily to treat the bacterial infection associated with periodontitis on a short-term, periodic basis. These treatments include mechanical and surgical techniques, prophylactic approaches, such as mouthwashes, and locally delivered therapies.

We note that a variety of drugs indicated for antimicrobial use are sometimes regulated under section 507 of the FDC Act and sometimes not. These include metronidazole, which is subject to section 505. The precise basis for why some anti-infectives are classified as antibiotics and others are not is unclear. The agency appears to have been inconsistent in defining drugs that are subject to section 507.

Other Relevant Information:

By way of background, CollaGenex submitted to FDA the referenced pending NDA for Periostat® on August 30, 1996. The Periostat® NDA was accepted for filing on October 29, 1996. When CollaGenex originally submitted the application it was designated as NDA No. 20-642. On September 16, 1996, however, CDER's Division of Dermatologic and Dental Drug Products (the "Division") informed the Company that the NDA number had been changed to 50-744, a reflection of the fact that FDA assigns the 50,000 series numbers to full antibiotic applications. Nonetheless, the application is currently being reviewed by the Division of Dermatologic and Dental Drug Products, not the

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Division of Anti-Infective Drug Products. Various FDA personnel have informed CollaGenex that its application is being handled and reviewed under section 507 of the FDC Act.

The Dental Drug Division advised CollaGenex when it filed the NDA that CollaGenex could request that the NDA be designated as a 505(b) application. The Company was also informed, however, that the submission of such a request at that time could significantly impede the agency's acceptance of the NDA for filing and substantive review. The Division also suggested that CollaGenex revise the applicable NDA cover letter and readdress the new drug/antibiotic designation issue once the NDA had been accepted for filing. Therefore, on September 17, 1996, CollaGenex submitted a revised cover letter and Form FDA 345h to reflect the new NDA number and to state that the NDA was submitted pursuant to section 507 of the FDC Act rather than section 505.¹ The Company is now addressing the antibiotic issue that is in dispute by the submission of this designation request. Although the agency component (CDER) is not in question, the product jurisdiction of Periostat® under section 507 is in dispute.

CollaGenex's Recommendation:

CollaGenex agrees that the agency component with primary jurisdiction for the review of the Periostat® NDA should be the Center for Drug Evaluation and Research, particularly the Division of Dermatologic and Dental Products, not the Division of Anti-Infective Drug Products. Given the mechanism of action of and the indicated use for the drug which is the subject of NDA 50-774, the Anti-Infective Division would not be the appropriate Division to review the subject NDA. CollaGenex also believes that the appropriate classification of its product is as a non-antibiotic drug subject to approval under section 505, not section 507, of the FDC Act, for the reasons discussed below.

¹ Certain written correspondence that CollaGenex received from FDA regarding ~~NDA 50-774~~ subsequent to that date states that the application was submitted pursuant to section 505(b) of the FDC Act. An action letter received on August 27, 1997, however, states that the NDA is not approvable under section 507 of the Act.

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The relevant provisions pertaining to this recommendation are sections 201(g) and 507(a) of the FDC Act, 21 U.S.C. §§ 355(g) and 357(a). Section 201(g) is pertinent because although section 507(a) defines an antibiotic, it does so in the context of the use of the word "drug." Section 507 refers to "any drug . . . for use by man" that has certain characteristics further defined by section 507(a). Section 507 therefore cannot be read in isolation. It must be read in conjunction with section 201(g), which defines the term "drug" that is referenced in section 507.

In pertinent part, section 201(g) of the FDC Act defines the word "drug" to mean an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease of man or other animals" (emphasis added). Therefore, whether a substance is a "drug" or "drug product" subject to section 507(a) depends on the product's intended use. FDA's regulations state that the words "intended use" or words of similar import refer to the objective intent of the manufacturer or other person legally responsible for the labeling of the product. 21 C.F.R. § 201.128 (1996).

Objective intent can be shown by, among other things, labeling claims, advertising materials, or oral or written statements of such persons or their representatives. *Id.*

A product subcategory which meets the statutory definition of a "drug" in section 201(g) is an "antibiotic drug" if it also meets the requirements of section 507(a). Under the FDC Act all antibiotics described in section 507 are drugs if they meet the requirements of section 201(g), but not all drugs are antibiotics. The importance of this distinction traditionally is that antibiotics can be subject to certification and other requirements, whereas most other drugs are not. More relevant today is the consideration that although antibiotics are subject to abbreviated applications,² they are not subject to the exclusivity provisions of Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 because they are not approved under section 505. See 57 Fed. Reg. 17950, 17951 (1992) and *Glaxo, Inc. v. Heckler*, 623 F. Supp. 89 (E.D.N.C. 1985).

² See 21 C.F.R. § 314.62.

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Section 507(a) of the FDC Act defines the term "antibiotic drug" to mean "any drug intended for use by man containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance)" (emphases added). It is unclear what the "intended for" language in section 507 adds, if anything, beyond that same language appearing in section 201(a) pertaining to the general definition of a drug. Thus, for a product to be categorized as an "antibiotic" drug, the rest of the language in section 507 states that two requirements must be met. The drug must both be produced by a microorganism (or be the synthetic equivalent thereof) and have the "capacity" to inhibit or destroy microorganisms "in dilute solution." In short, the definition is two-pronged, stating that status of a compound as an antibiotic is dependent both on its source or, in the case of a synthetic product, on its chemical structure, and its microbial activity in "dilute solution."

Periostat® does not meet the statutory "antibiotic drug" provisions of sections 201(a) and 507(a). It neither is intended for use as an antimicrobial agent nor does it actually have the capacity to inhibit or destroy microorganisms at the recommended dosage levels that are used to treat periodontitis. The clinical and nonclinical studies described in the "Mechanism of Action" section of the Periostat® NDA, which are reflective of objective intent, clearly demonstrate that the only active ingredient in the drug product, doxycycline hyclate, is for use in the treatment of periodontitis in a manner which is not dependent upon the inhibition or destruction of microorganisms.

In terms of the "source" aspect of the first prong of the antibiotic definition, doxycycline is synthetically produced and is not obtained from microbial sources. Periostat® does not contain any quantity of a drug derived from a microbe, particularly since microbes do not produce doxycycline. Further, doxycycline is not the "chemically synthesized equivalent" of oxytetracycline. Doxycycline is chemically different from oxytetracycline. Although doxycycline is derived from oxytetracycline, which is obtained from microorganisms, this fact should not trigger the source requirement of the definition. Section 507(a) does not state that any use of a microorganism to produce a drug renders the drug an antibiotic. For example, the use of a microorganism to produce an intermediate or a precursor of a drug, including active or inactive components, should not render the product an antibiotic. If it did, this interpretation

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would ignore the actual language of the statute. Moreover, such an interpretation would require the agency to engage in a thorough investigation of the source of every component used in the manufacture of a drug, perhaps even for those that do not actually appear in the final drug product.

Undue emphasis on the "source" prong of the antibiotic definition can be problematic for other reasons. In this age of modern genetic techniques, microorganisms can produce a variety of substances such as hormones, insulin, and other drugs. Then, too, biological drugs that are regulated under section 351 of the Public Health Service Act, 42 U.S.C. § 262, could also be classified as antibiotics under this prong of the definition. See Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research (CBER), at p. 5 (excepting products of cell culture from CBER regulation that are antibiotics). Further, although antibiotic regulation was established in 1945 when there was insufficient knowledge and control of fermentation processes and methods of analysis,³ substantial advances in manufacturing and assay methods have occurred. The current lack of any certification requirements for antibiotics is testimony to these advancements. See 21 C.F.R. § 433.1 (1996). Indeed, the antibiotic provisions, as originally enacted, anticipated developments that would make antibiotic certification unnecessary. See Statement of Watson B. Miller, May 15, 1945, on H. Rept. No. 702, 79th Cong., 1st Sess., reprinted in Senate Reports, 79th Cong., 1st Sess., at p. 11. For this reason, provisions were enacted in 1945 and still are contained in the law today that allow for FDA to exempt antibiotic drugs from any of the requirements of section 507. See section 507(c), 21 U.S.C. § 357(c).

These and other considerations discussed below indicate that whatever relative importance the "source" prong of the antibiotic definition may once have had vis-à-vis the second prong of the definition, such importance seems to have waned considerably. The substantive and distinguishing aspect of the definition in section 507(a) therefore pertains to the second prong, the capacity of a drug to inhibit or destroy microorganisms "in dilute solution." Since this quoted language is not defined in the statute or in FDA's regulations, nor does there appear to be relevant legislative

³ See, e.g., Senate Rep. No. 1744, Views of Senators E. McKinley Dirksen and Ramon L. Hruska, reprinted in 1962 U.S. Code Cong. & Adm. News 2884, 2928.

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history on the topic, we can only presume what may have been intended. The language seems to refer to some inherent capacity of a chemical to exert an antimicrobial effect, even when "diluted." Many chemicals can have antimicrobial effects at "high" doses, whether derived from microorganisms or not. To repeat a trite, but relevant phrase, "The dose is the poison." In the present situation, we cannot help but feel therefore that this quoted language, coupled with the intended use language of section 201(a), is a reference to the dosage level at which drugs are administered. Indeed, even classical antibiotics, such as erythromycin or penicillin, will not inhibit or destroy microorganisms to any clinically significant degree if they are sufficiently diluted. Similarly, in the "dilute solution" of the recommended dosage levels of 20 mg b.i.d., Periostat® does not have the capacity to inhibit or destroy microorganisms.

Finally, we note also that the Clinton Administration and FDA in a report entitled "Reinventing the Regulation of Drugs and Medical Devices" (April, 1995) both are committed to repealing section 507. All antibiotics would formally be made subject to regulation under section 505. Indeed, the practical reality today is that antibiotics already are regulated like other drugs subject to section 505. We therefore wish to emphasize the significant competitive anomaly posed by section 507 status for Periostat®. Without Title I exclusivity, Periostat® will be subject to generic competition immediately upon publication of a relevant antibiotic monograph. CollaGenex has invested \$14 million in the development of its drug for periodontal use. An adverse decision will enable competitors to copy Periostat® and will force CollaGenex to spend millions of dollars more in defending its patents covering Periostat®. It also will likely discourage further product innovation in the anti-infective area. The potential of these additional costs could prove devastating to CollaGenex as a small company.

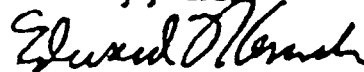
In light of the foregoing facts and premises considered, Periostat® is not — and should not be treated as — an antibiotic drug within the meaning of sections 201(a) and 507(a) of the FDC Act. CollaGenex therefore respectfully requests that FDA designate the Periostat® NDA that has been accepted for filing by the Division of Dermatologic and Dental Drug Products as subject to the new drug provisions of section 505, not section 507, of the FDC Act.

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Please do not hesitate to contact me if you have any questions regarding this request for designation, if you need additional information, or if you would like to meet with us to discuss this matter further.

Cordially yours,



cc: Mr. Christopher V. Powala,
CollaGenex Pharmaceuticals, Inc.

(FAX COPIES WILL BE REFUSED)

January 9, 1998

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Effect of Sub-Antimicrobial Dose Doxycycline on Periodontal Microbial Resistance I. THOMAS*, C. WALKER, A. CROUT, R. METHENY, J. KARAKIOZIS, J. WETZEL, C. POWALA, and M. BRADSHAW (WVU, Morgantown, WV; UF-PDRC, Gainesville, FL; CollaGenex, Newtown, PA).

A multi-center, double-blind, placebo-controlled study was conducted to determine if sub-antimicrobial dose doxycycline (SDD) administered orally for 9-months as 20 mg b.i.d. resulted in an increase in doxycycline resistance or multi-antibiotic resistance of the periodontal microbiota. Seventy-Eight (78) adult periodontitis subjects were enrolled. Each subject received scaling and root planing (SRP) in the 2 qualifying quadrants and were then randomly assigned to receive either SDD or placebo treatment. Plaque samples were collected at baseline (BL), 3, 6, and 9 months, from two separate tooth sites within the SRP quadrants and from 2 sites in the non-SRP quadrants using the sterile endodontic paper point method. Tooth sites from which plaque samples were obtained must have had BL PPD of ≥ 5 to ≤ 9 mm. Plaque samples were pooled by subject as to SRP or non-SRP treatment and were plated on general purpose growth medium containing 4 $\mu\text{g/mL}$ doxycycline (upper limit of "Susceptible"). The 3 most numerous colony types were individually enumerated and expressed as a percent of the total doxy-resistant bacteria cultivated. A representative of each of the 3 colony types was subcultured, identified and its MIC was determined for each of 6 antibiotics (doxycycline, minocycline, tetracycline, amoxicillin, erythromycin, and clindamycin). The results obtained for each treatment at each sample period were examined to determine if differences existed either in distribution of doxycycline-resistance or in the bacteria expressing resistance. Five taxa (*Streptococcus*, *Prevotella*, *Flavobacterium*, *Campylobacter*, and *Bacteroides*) accounted for 80% of the doxycycline-resistant isolates. These resistant isolates persisted throughout the study and were distributed similarly within each treatment group. There were no statistically (p -value < 0.05) or microbiologically significant differences between treatment groups at any post-BL visit. We conclude that a 9-month course of SDD treatment did not result in either the acquisition of doxycycline-resistance or multi-antibiotic resistance in the periodontal microbiota nor did its use result in overgrowth by doxycycline-resistant bacteria. Supported by CollaGenex Pharmaceuticals, Inc.

Effect of Sub-Antimicrobial Dose Doxycycline on Periodontal Flora. C. WALKER*, A. HEFTI, J. THOMAS, S. NANGO, J. LENNON, J. WETZEL, and C. POWALA (UF-PDRC, Gainesville, FL; WVU, Morgantown, WV; CollaGenex, Newtown, PA).

A multi-center, double-blind, placebo-controlled study was conducted to determine if sub-antimicrobial dose doxycycline (SDD) therapy, administered orally for 9-months as 20 mg b.i.d., exerted an antimicrobial effect on the subgingival microflora. Adult periodontitis subjects ($n=78$) with baseline probing pocket depth (PPD) ≥ 5 to ≤ 9 mm in at least 3 quadrants were enrolled. Each subject received scaling and root planing (SRP) in 2 quadrants and was randomly assigned to receive either SDD or placebo treatment. Microbial samples were collected at baseline (BL), 3, 6, and 9 months from 2 separate tooth sites within the SRP quadrants and from 2 sites in the non-SRP quadrants. Each sample site was required to have a BL PPD of ≥ 5 to ≤ 9 mm. The samples were pooled per subject by SRP or non-SRP treatment, examined by darkfield microscopy, and enumerated on selective and non-selective media. Significant reductions ($p < 0.05$) were detected in the proportions of spirochetes present in the SRP/SDD-treated subjects at 3, 6, and 9 months and in the non-SRP/SDD group at month 9 compared with placebo. Analyses of the clinical indices for the sample sites revealed a mean attachment level (AtL) gain of 1.4 mm, a PPD decrease of 1.6 mm and a 22-39% decrease in BOP in the SRP/SDD subjects compared with values of 0.9 mm, 1.1 mm, and 2-16%, respectively for the SRP/placebo subjects. No significant differences ($p < 0.05$) were detected between SDD and placebo groups in total cultivable anaerobic flora, in the recovery of periodontal pathogens, or in the recovery of opportunistic pathogens including *Candida*. Since there were no significant differences in other bacterial groups with sensitivities similar to the spirochetes and since the latter are often associated with gingival inflammation, it was hypothesized that the reduction in spirochetes was a result of improvements in the periodontal pockets rather than a direct antimicrobial effect. We conclude that the long-term administration of SDD had no detrimental effect on the periodontal flora and did not result in either an antibiotic-induced shift in its composition or in overgrowth by periodontal and/or opportunistic pathogens. Supported by CollaGenex Pharmaceuticals, Inc.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-744

SEP 30 1998

CollaGenex Pharmaceuticals, Inc.
Attention: Christopher Powala
Director, Drug Development and Regulatory Affairs
301 South State Street
Newtown, PA 18940

Dear Mr. Powala:

Please refer to your new drug application (NDA) dated August 30, 1996, received August 30, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Periostat™ (doxycycline hyclate USP) Capsules, 20 mg. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated August 28, October 1, November 13, December 8, 1997; January 6, 14, and 19, February 10, March 2, 18, and 31, April 23 and 28, July 9 and 29, and September 3, 14, 16, 22, 24 (2), and 25, 1998. Your submission of March 31, 1998 constituted a full response to our August 27, 1997, action letter. The user fee goal date for this application is October 1, 1998.

This new drug application provides for the use of Periostat™ (doxycycline hyclate USP) Capsules, 20 mg as an adjunct to subgingival scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. We acknowledge your commitment made in the teleconference with this Division on September 16, 1998, to revise the carton and container labeling so that the prominence of the established name and tradename is commensurate and in accordance with 21 CFR 201.10(g)(2).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 50-744". Approval of this submission by FDA is not required before the labeling is used.

NDA 50-744

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We remind you of your Phase 4 commitments agreed to in your submissions dated August 3, 1998, and September 14, 1998. These commitments, respectively, are listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each clinical study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

NDA 50-744

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If you have any questions, contact Roy Blay, Ph.D., Project Manager, at (301) 827-2020.

Sincerely,

/S/

Jonathan K. Wilkin, M.D.

Director

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

Enclosure

Nov-19-02 10:03 From-

1-793 P.23/23 F-263

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

COLLAGENEX PHARMACEUTICALS, INC.,
Plaintiff,

v.

Civ. Case No. 03-01405 (RMC)

TOMMY G. THOMPSON, Secretary of Health
and Human Services, DEPARTMENT OF
HEALTH AND HUMAN SERVICES,
MARK B. McCLELLAN, Commissioner of
Food and Drugs, and FOOD AND DRUG
ADMINISTRATION, Defendants,

MUTUAL PHARMACEUTICAL
COMPANY, INC., Intervenor-Defendant,

and

WEST-WARD PHARMACEUTICAL CORP.,
Intervenor-Defendant.

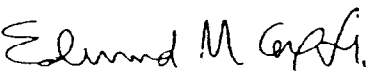
DECLARATION OF EDWARD M. COX, Jr.

Edward M. Cox declares as follows:

1. I am Deputy Director, Office of Drug Evaluation IV, Office of New Drugs, Center for Drug Evaluation and Research, United States Food and Drug Administration (FDA).
2. In this capacity, I have custody of official records of FDA.
3. Attached is a copy of the administrative record pertaining to FDA's classification of Periostat® (doxycycline hyclate) 20mg as an antibiotic drug.
4. Copies of the administrative record are part of the official records of FDA.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on September 23, 2003.



Edward M. Cox, Jr., M.D. M.P.H.